

## **REMARKS**

Applicant respectfully requests reconsideration and allowance of all pending claims.

### **I. Status of the Claims**

In this Response to the final Office action, no claims have been amended. Accordingly, claims 1 and 3-25 remain pending.

### **II. 35 U.S.C. 103(a) Rejection**

Reconsideration is requested of the rejection of claims 1 and 3-25 under 35 U.S.C. §103 as being obvious in view of Hofstadter (U.S. Patent No. 4,317,903).

#### **A. The Claimed Subject Matter**

The present application is generally directed to a novel industrial process for recovering pure fentanyl from an impure preparation of fentanyl containing phenethylpiperaniline. More particularly, as currently pending, the independent claims of the present application are directed to an industrial process for recovering pure fentanyl, which as defined in the claims includes a phenethylpiperaniline impurity level of less than 0.010 weight percent, from an impure preparation comprising fentanyl containing phenethylpiperaniline. The process comprises subjecting the impure preparation to a reverse-phase high performance preparative liquid column chromatography, wherein a loading ratio of column media to fentanyl loaded onto the column is in the range of from about 50 to about 150.<sup>1</sup>

As noted in the present application (see, e.g., paragraph [0015]), Applicant discovered the claimed process can be employed, for example, using a series of

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<sup>1</sup> As noted on page 5 of the specification (paragraph [0019]), "loading ratio" is the weight ratio of the stationary phase to the fentanyl loaded thereon; that is, it is a weight ratio of column media to fentanyl.

collected fractions, which may be partially recycled, to obtain a purified fentanyl in a high yield. Specifically, fentanyl is produced with phenethylpiperaniline impurity levels less than 0.010 weight percent in the purified product. Furthermore, Applicant discovered the present process is particularly advantageous as compared, for example, to analytical HPLC, which would require a loading ratio significantly higher than the range recited here (see, e.g., paragraph [0029]).

### **B. The Cited Art**

Hofstetter discloses methods of using a reverse-phase high performance preparative liquid chromatography to obtain a highly pure preparation of the antibiotic lincomycin hydrochloride. The methods generally comprise a number of steps, including: (a) dissolving approximately 450 grams of the starting material (i.e., impure preparation of lincomycin A and lincomycin B) per liter of 30% aqueous methanol; (b) applying the solution to a chromatography column filled with 18 grams of C<sub>18</sub> bonded phase silica gel per gram of starting material; (c) stripping the remaining lincomycin from the column with 1 bed volume of methanol; (d) concentrating the lincomycin-rich eluate to dryness; (e) crystallizing the lincomycin according to standard crystallization procedure; (f) re-chromatographing the lincomycin B-rich fraction according to the above procedure; (g) concentrating the eluate containing greater than 98% lincomycin B to dryness; and (h) re-dissolving the solids in 3 milliliters of methanol per gram of lincomycin B solids at 40°C and adjusting the pH with concentrated hydrochloric acid to 1.5. Notably, Hofstetter states that the weight ratio recited in step (b) is "near optimum"; that is, Hofstetter states that the weight ratio of silica gel (i.e., the column media) to lincomycin is "near optimum" at 18:1.

### **C. The Claimed Subject Matter is Not Obvious**

In order for the Office to show a *prima facie* case of obviousness, M.P.E.P. §2142 requires a clear articulation of the reasons why the claimed invention would have been obvious. Specifically, to reject a claim based on this rationale, the Office must

articulate the following: (1) a finding that there was some teaching, suggestion, or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at each and every limitation of the claimed invention; (2) a finding that there was reasonable expectation of success; and (3) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. Applicant respectfully submits the Office has failed to establish a prima facie case of obviousness because each and every element of the claims has not been disclosed or suggested by the cited reference, and/or because there is no motivation to modify the reference in order to achieve the claimed subject matter.

Applicant submits that nowhere in the cited reference is a process for producing pure fentanyl disclosed or suggested. In fact, Hofstetter does not even mention fentanyl; rather, Hofstetter discloses the recovery of lincomycin. Lincomycin is a compound that is distinctly different structurally from fentanyl. There is simply no reason for one of ordinary skill in the art to look to a reference, such as Hofstetter, which teaches a completely different compound for a method of purifying fentanyl. More specifically, one of ordinary skill in the art simply would not think to look to the method of Hofstetter, and further, modify the operating conditions of Hofstetter's method, to arrive at the method of Applicant's claim 1. With all due respect, it appears that the Office has used hindsight reconstruction, using the Applicant's invention as a blueprint, to find the instant claim 1 obvious. The Federal Circuit has repeatedly ruled against this type of analysis.

In support of Applicant's position, and as further detailed in the Background of the specification, it is to be noted that prior to the instantly claimed invention precipitation and recrystallization were typically used for purifying fentanyl. In further support of Applicant's position, the Office's attention is called to the declaration of the sole inventor, Enrico Anthony Antonini, which is being submitted simultaneously with the present Response. Mr. Antonini states that, if provided with the prior attempts of using recrystallization methods and the difficulties with analytical chromatography (as described herein with respect to narcotics), one of ordinary skill in the art would look to

methods of improving the recrystallization process for purifying fentanyl. One of ordinary skill in the art would not look to chromatography methods, and certainly would not look to the chromatography method used by Hofstetter because Hofstetter is directed to purifying a compound that is very different structurally as compared to fentanyl.

Furthermore, nowhere does Hofstetter disclose or suggest a process for obtaining a "pure" product, wherein the concentration of the impurity of concern or interest (i.e., phenethylpiperaniline) therein is less than about 0.010 weight percent; rather, Hofstetter is only concerned with limiting the concentration of lincomycin B to less than about 0.5 weight percent, which is significantly higher (i.e., 50 times higher) than the limit recited in the present claims.

Finally, nowhere in the cited reference is a loading ratio of column media to fentanyl (or, in Hofstetter's case, lincomycin) in the range of between about 50 and about 150 disclosed or suggested. In fact, Hofstetter's statement that the disclose ratio of 18:1, which is more than 2.5 times less than the recited minimum of "about 50", is "near optimum" arguably teaches away from the recited ratio.

In the final Office action, the Office states that Applicant's arguments are unpersuasive as the process of purification of organic chemicals by reverse phase high performance chromatography is well known in the art, and further, as Applicant admits, "in general, preparative liquid chromatography is a well known and understood separation technique." Accordingly, the Office states that optimization of loading ratio, solvent systems, recycling, etc. based on the results of analytical hplc data, for the scale-up for preparative chromatography method is within the ability of one of ordinary skill in the art. Applicant respectfully disagrees. As noted in the Background of the instant specification, while numerous organic materials have been separated or purified by means of the chromatographic process, in most instances, the conditions under which the chromatographic separation was carried out was not indicated. Furthermore, as noted in paragraph [0007], any use of analytical chromatography on narcotics, such as fentanyl, would likely guide an individual of ordinary skill in the art away from using preparative chromatography for an industrial scale process, such as claimed in the

instant invention. Specifically, analytical chromatography on narcotics typically requires loading an infinitely small mass of a feed onto a column, and using a small particle size (typically less than 5 micrometers) in the stationary phase. This small particle size generates much higher pressures than those found in typical preparative chromatography methods, mandating the use of very large, strong and expensive chromatography equipment, which would negate the commercial viability for this analytical process. Furthermore, in conventional preparative chromatography, the particle size of the stationary phase is small enough to achieve the separation, but is much larger than that used for analytical chromatography (typically greater than 20 microns).

In view of the foregoing, Applicant respectfully submits that the cited reference fails to disclose or suggest each and every limitation of the claims. Applicant additionally submits that there is simply no motivation to modify the cited reference in order to achieve the claimed subject matter, because Hofstetter teaches a compound very different structurally from fentanyl, and because Hofstetter teaches away from the recited loading ratio. Applicant therefore submits the present rejection is improper, and accordingly request reconsideration and allowance of all pending claims.

### **III. Double Patenting Rejection**

While the Double Patenting Rejection was not maintained in the final Office action, Applicant believes that the Rejection was mistakenly not included. Specifically, Applicant notes that all pending claims were previously rejected on the ground of nonstatutory obviousness-type double patenting in view of the pending claims of copending U.S. Patent Application Serial Nos. 10/501,353, 11/576,059, and 11/916,036. Applicant maintains that this rejection is a provisional obviousness-type double patenting rejection, since the applications have not yet issued as patents. Accordingly, Applicant respectfully reserves the right to address the merits of this rejection, as appropriate, if the listed applications issue as patents before the application at hand.

**CONCLUSION**

In view of the foregoing, Applicant respectfully requests favorable reconsideration and allowance of all pending claims.

The Commissioner is hereby authorized to charge Deposit Account 13-1160 for any fees due for the submission of this Response to Final Office Action, and/or for the Request for Continued Examination and Declaration of Mr. Antonini being filed simultaneously herewith.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Craig D. Siman', with a long horizontal flourish extending to the right.

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